Original Article

Melatonin Effects in Methylphenidate Treated Children with Attention Deficit Hyperactivity Disorder: A Randomized Double Blind Clinical Trial

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Objective: The aim of this study was to determine melatonin effects on sleep patterns, symptoms of hyperactivity and attention deficiency in children with attention-deficit hyperactivity disorder (ADHD).
Methods: Children with age range of 7-12 years who had a combined form of ADHD were randomly divided in to 2 groups according to gender blocks. One group took melatonin (3 or 6mg) combined with methylphenidate (Ritalin) (1mg/kg), and the other group took placebo combined with methylphenidate (1mg/kg). ADHD rating scale and sleep patterns questionnaires were completed. Research hypotheses were assessed at the baseline, the second, fourth and eighth weeks after the treatment.
Results: The mean sleep latency and total sleep disturbance scores were reduced in melatonin group, while the scores increased in the placebo group ($p \geq 0.05$). Data analysis, using ANOVA with repeated measures, did not show any statistically significant differences between the two groups in ADHD scores.
Conclusion: Administration of melatonin along with methylphenidate can partially improve symptoms of sleep disturbance. However, it does not seem to reduce attention deficiency and hyperactivity behavior of children with ADHD.

Key words: *Attention deficit disorder with hyperactivity Disorder, Child, Melatonin, Methylphenidate, Sleep*

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Approximately 25-50% of patients with attention-deficit hyperactivity disorder (ADHD) have sleep problems (1-3). Moderate to severe sleep problems are more common in ADHD children compared to other psychiatric controls and healthy pediatric controls (4).
It has been reported that children with ADHD may suffer from insomnia more than twice compared to pediatric controls (4, 5). Unfortunately, more severe and more prevalent sleep problems occur in stimulant treated ADHD children than in untreated children with ADHD (4-7). Stimulant taking ADHD children displayed roughly a two-fold increase in sleep onset latency or insomnia compared to untreated children with ADHD (4, 5). Daytime indications of ADHD may be influenced adversely by sleep disturbance side effects of methylphenidate (8). In fact, sleep disturbances may exacerbate ADHD symptoms including irritability. Therefore, any intervention aiming sleep promotions in these children may subside ADHD symptoms (2).
Melatonin is formed from an essential amino acid tryptophan via serotonin pathway (9, 10). Melatonin synthesis is stimulated in darkness and is reduced by light. It is an antioxidant molecule, which reduces other antioxidants and has scavenger properties (11). Furthermore, the major role of melatonin in the human body is to regulate sleep-wake cycle (12, 13).
Melatonin can also be taken as an exogenous supplement, which is chemically identical to its endogenous supply, and is classified as a natural health product by Health Canada or dietary supplement by the United States Food and Drug Administration. Due to its involvement in the sleep cycle, melatonin supplement has been investigated extensively for sleep disorders (14, 15). Uses of melatonin supplement is very interesting and safe compared to other sleep medications (12).
Therefore, we decided to evaluate the effects of melatonin on sleep patterns, attention deficiency and

hyperactivity behavior of methylphenidate treated children who suffer from ADHD.

Materials and Method

Participants

Children aged 7-12 years who were diagnosed with ADHD (combined form) by a child and adolescent psychologist and did not use any confounding drugs or supplements were recruited into the initial stage of this study. Children with history of major prenatal complications such as prematurity, low birth weight (reported by parents), any past or present psychosis, comorbid tourette syndrome, celiac, phenylketonuria, autism, or other persistent developmental disorders were excluded. Furthermore, narcotics use was among our exclusion criteria.

Parents of 60 ADHD children who met the inclusion criteria signed the consent forms and oral assent was attained from children. Eight children (25%) in the placebo group and 2 (7.25%) in the melatonin group dropped out of the study voluntarily or were excluded due to irregular drug consumption. Finally, 26 children in the melatonin group and 24 in the placebo group completed the study.

Procedure

In the first visit, personal and demographic questionnaires, special tests for ADHD (ADHD Rating Scale: based on diagnostic criteria for DSM-IV), and SDSC (Sleep Disturbance Scale for Children) questionnaire were completed by mothers. Then, anthropometric measurements in standard situation were performed. Children were then divided into two groups in a double blind permuted block randomized allocation design based on gender blocks. One group took melatonin (3or6mg based on weight: 3mg in children under 30kg and 6mg in those above 30kg according to Kristiaan and colleagues(16)) combined with methylphenidate (Ritalin) (1mg/kg), and the other group took placebo combined with methylphenidate (1mg/kg). Methylphenidate, (10mg tablets, Basel, Switzerland), Melatonin (3mg capsules, Nutricenturi, Canada), and Placebo (starch capsule, made by Institute of Medicinal Plants, Tehran, Iran) were used in this study.

ADHD rating scale and SDSC sleep questionnaires were completed by mothers at baseline, and were repeated at 2, 4, and 8 weeks after beginning of the treatment. Anthropometric assessments were done and repeated 8 weeks after the treatment. At the end of study, the stimulant drug side effects questionnaire was completed by mothers. Side effects were then compared between the two trial groups.

This study was approved and licensed by Clinical Ethics Board of Tehran University of Medical Sciences (Letter No. 31807).

Statistics

The sample size was determined so that researchers could detect at least 25 minute change in sleep latency with a power of 80% and to detect type I error of 5%. Based on these calculations, the number of 18 children was determined to be sufficient but the sample collection was continued to cover more than 20% case loss which is common in clinical trials. The results were compared between the two groups using SPSS software version 17, and ANOVA with repeated measures analysis. Demographic parameters were compared between the two groups using Independent Sample t-test (for quantitative variables), Chi-Square and Fisher's Exact Test (for qualitative variables).

Questionnaires Features and Norm Finding

ADHD Rating Scale is an 18 item likert-type scoring system which ensures internationally validated and standardized criteria in the assessment of ADHD. This scale is designed based on DSM-IV criteria. There is unanimity among psychiatrists and researchers on using this questionnaire for diagnosing ADHD (17). This rating scale consists of two sub scores by which inattention behaviors and hyperactivity behaviors are separately recognizable. A total score for assessing ADHD is given by summing up these sub scores. (18).

SDSC is a standardized 27 item likert-type scoring system for assessing different aspects of sleep disturbances in children and adolescents. Sleep duration, sleep latency, and 6 common sleep disorders in childhood and adolescence (including: Disorder of initiating and maintaining sleep, sleep breathing disorders, disorders of arousal nightmares, sleep wake transition disorders, disorders of excessive somnolence, and sleep hyperhydrosis) are distinguishable using this questionnaire. Summation of these sub scores gives a total score which has been used in this article to compare sleep disturbances between the two trial groups (19).

The validity and reliability of SDSC questionnaire were evaluated and verified again by the research team. First, translation and post-translation were done. Content validity was then approved by a committee of psychiatrics and psychologists. The questionnaire was subsequently completed by 20 volunteers, and cronbach's alpha of 0.85 was earned. The test was retested 2 weeks later, and p value of 0.24 was then attained using paired t-test analysis.

Results

Mean age of children was 9.57±1.65 in the melatonin group, and 8.83±1.82 in the placebo group, but the difference was not statistically significant according to independent sample t-test (P=0.138). Maternal age at delivery time was 26.4 in the melatonin group, and it was 25.2 in the placebo group, but this difference was not statistically significant (p=0.381). Other demographic variables and tests of similarity of distribution between the two trial groups are listed in Table 1. Attention deficiency (Figure 1) and hyperactivity (Figure 2) were separately evaluated based on ADHD rating scale questionnaire. Total sleep duration (Figure 3), sleep latency (Figure 4), and total

sleep disturbance score (Figure 5) were evaluated based on SDSC sleep questionnaire. The tests were done at baseline and were repeated at 2, 4, and 8 weeks after the treatment. The results were compared between two trial groups by using ANOVA with repeated measures. At the end of 8th week of the trial, Stimulant Drug Questionnaire was completed voluntarily by mothers. Twenty subjects in melatonin group and 18 in placebo group completed this questionnaire. The results are listed in table 2. Mean scores of side effects based on the stimulant drug side effects questionnaire were 11.35±8.81 in melatonin group and 10.16±9.05 in placebo group. This difference was not statistically significant (p=0.686).

Discussion

Methylphenidate is almost 75% effective in treating ADHD (20, 21). However one of its most common complications, which are usually regarded unfavorably by parents, is sleep disturbances (5, 22, 23). Sleep disorders generally play an important role in the decline of cognitive functions (24, 25). Because cognitive performance can be improved by managing and controlling the sleep-waking cycle (25), we hypothesized that by improving sleep patterns, it may be possible to make an improvement in hyperactivity or at least in attention deficiency of children with ADHD. Nevertheless, in this study, we were not able to observe any significant differences in attention deficiency or hyperactivity between the two groups. This result is similar to that of Kristiaan(16) and Margaret (26).

These findings may shed some light on the catecholaminergic mechanism of ADHD (27).

Table 1: Similarity of distribution of demographic variables between Melatonin plus Methylphenidate (Melatonin) & Placebo plus Methylphenidate (Placebo) Groups

Demographic variable	N		Percent		χ^2
	Melatonin	Placebo	Melatonin	Placebo	
Gender					
Girl	7	7	26.9	29.2	*p =0.786
Boy	19	17	73.1	70.8	
Level of family income					
Low	8	10	47.1	58.8	
Average	5	4	29.4	23.6	*p =0.492
High	4	3	23.5	17.6	
Children delivery type					
Cesarean	14	11	58.3	52.4	*p =0.688
Natural	10	10	41.7	47.6	
Parents relationship					
Divorced	1	3	4.0	14.3	*p =0.217
Not divorced	24	18	96.0	85.7	
Child birth order					
First	14	15	58.3	65.2	
Middle	3	3	12.5	13.1	*p =0.726
Last	7	5	29.2	21.7	

Data have been missed in some categories

*: Fisher's Exact Test

Table 2: Stimulant drug side effects; comparison between Melatonin plus Methylphenidate (Melatonin) & Placebo plus Methylphenidate (Placebo) groups at 8 weeks after beginning of the treatments

Drug side effects	Melatonin		Placebo	
	N	%	N	%
Loss of appetite	14	70.0	11	61.1
Weight loss	9	45.0	9	50.0
Stomachache	9	45.0	5	27.8
Dry moth	6	30.0	7	38.9
Nausea & vomiting	3	15.0	3	16.7
Irritability	16	80.0	10	55.6
Sadness	10	50.0	2	11.1
Headache	8	40.0	4	22.2
Difficulty falling sleep	8	40.0	8	44.4
Sleepiness	4	20.0	4	22.2
Acne	2	10.0	2	11.1
Dyskinesia	0	0.0	2	8.3
Tics	1	5.0	1	4.2

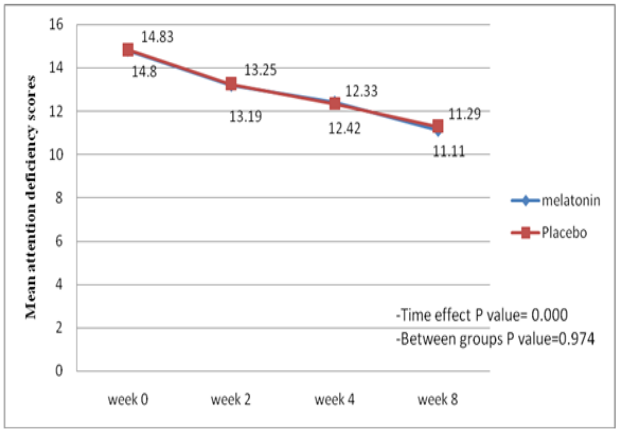

Figure1. Mean attention deficiency scores of two trial groups based on ADHD (attention-deficit hyperactivity disorder) rating scale at baseline, 2, 4 and 8 weeks after the treatment using ANOVA with repeated measures

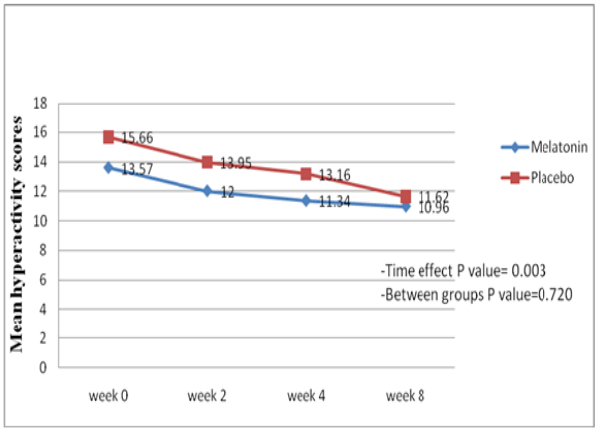

Figure 2. Mean hyperactivity scores of two trial groups based on ADHD rating scale at baseline, 2, 4 and 8 weeks after the treatment using ANOVA with repeated measures.

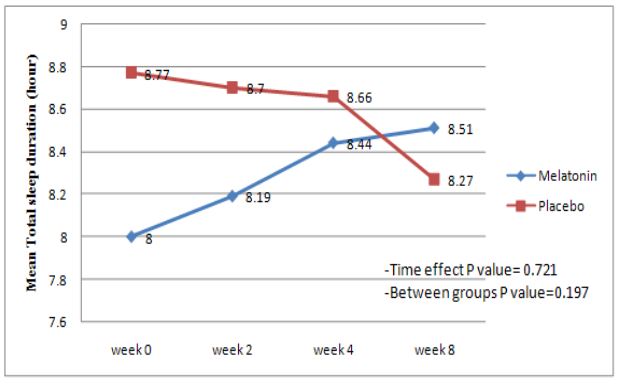

Figure3. Mean total sleep duration (hour) of two trial groups based on SDSC sleep questionnaire at baseline, 2, 4, and 8 weeks after the treatment using ANOVA with repeated measures.

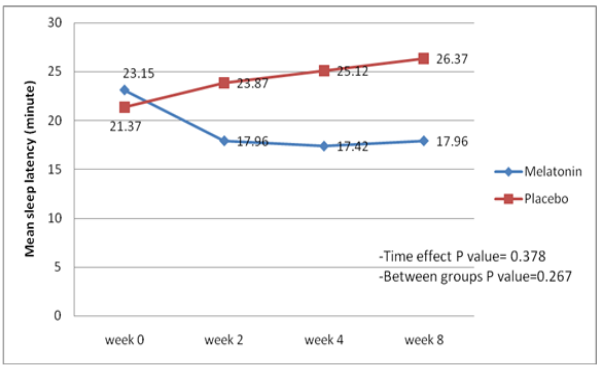

Figure 4. Mean sleep latency (minute) of two trial groups based on SDSC sleep questionnaire at baseline, 2, 4, and 8 weeks after the treatment using ANOVA with repeated measures

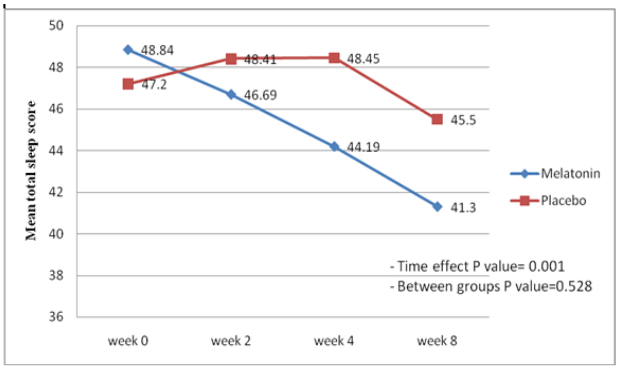

Figure 5. Mean total sleep score of two trial groups based on SDSC sleep questionnaire at baseline, 2, 4, and 8 weeks after the treatment using ANOVA with repeated measures.

Based on the results of this study, it may be inferred that defect in catecholamine receptors may cause the brain to fall asleep at a later time, but this might not be the case for a reverse situation.

It means that we can not fix the catecholamine receptor impairments by regulating sleep patterns and circadian rhythm. As a matter of fact, an ADHD-like behavior can be seen in some children with sleep disorders. Also, cognitive function and attention are decreased in sleep deprived children. This situation can be seen in some disorders such as celiac, epilepsy and in some sensitivity to artificial food colors and preservatives. However, these disorders should be discriminated from the real ADHD with catecholaminergic mechanism (28, 29).

Mean scores of sleep latency in melatonin group decreased while it had an increasing trend in placebo group in the context of time, but no statistically significant differences were observed between the two groups in the study period. Margaret Weis and colleagues, (2) in the study of "Sleep Hygiene and Melatonin Treatment for Children and Adolescents with ADHD and Initial Insomnia" showed a significant difference in sleep latency scores from polysomnography between the melatonin and placebo groups. The mentioned study was completely different from ours in design and cases. One of the inclusion criteria in the mentioned study was baseline sleep latency of more than 60 minutes. The other difference was the sleep hygiene season prior to their clinical trial which affected the results as a stable confounder. These two basic points may be the reasons for reaching a sharp and significant result. In our study, to generalize the results to a grater ADHD population, we emitted initial sleep latency defect criteria from the study design. Furthermore, to eliminate the stable confounding effects of sleep hygiene, we postponed the season until the end of our study.

Metabolic and neurological pathways of both ADHD and sleep disturbances need further clarification in future studies. In addition, more investigation is needed to target and treat ADHD and sleep problems simultaneously.

Conclusion

In this study, it was revealed that Melatonin with Methylphenidate can partially improve symptoms of sleep disturbance by circadian cycle modification. However, it did not seem to reduce the attention deficiency and hyperactivity behavior of ADHD children.

Conflict of Interest

Authors declare no conflict of interest related to this work.

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